Antidepressants

Depression

A World Health Organization (WHO) Prediction

- Depression is currently the 4th most significant cause of suffering and disability worldwide and, sadly, It will be the 2nd most debilitating human condition by the year 2020.

Chemical "Jobs"

Dopamine

- Attention
- Pleasure
- Emotions
- Reward
- Motivation
- Movement

Norepinephrine

- Alertness
- Observance
- Daydreaming
- Heart/BP rates
- Stress

Serotonin

- Regulates mood
- sleep
- emesis
- sexuality
- Appetite
- impulsiveness/ aggression

Depression

- **Symptoms:**
- **Cognitive**
  - Thoughts of hopelessness, poor confidence, negative thoughts. –
- **Emotional**
- Feeling sad, unable to feel pleasure, irritability
- **Psychomotor/Physical**
- • Decreased libido, energy
  • Sleep changes (70% less, 30% more)
  • Appetite changes (70 % less, 30 % more)

TX:

- Antidepressant Medications

– Selective serotonin reuptake inhibitor (SSRI's) are first line of treatment (gold standard).

- Psychotherapy
- Usually individual psychotherapy
- Cognitive behavioral therapy has most evidence for efficacy of treatment.
- **Sometimes exercise or body awareness has been found to helpful.**

Monoamine hypothesis of depression

- The monoamine hypothesis grew originally out of associations between the clinical effects of various drugs that cause or alleviate symptoms of depression and their known neurochemical effects on monoaminergic transmission in the brain.
- The monoamine hypothesis of depression suggests that depression is related to a deficiency in the amount or function of cortical and limbic serotonin (5-HT),norepinephrine (NE), and dopamine (DA).
- The chronic activation of monoamine receptors by antidepressants appears to increase in BDNF transcription.

Drug	Brand	Class	2007 Prescriptions (in millions)
Sertraline	Zoloft	SSRI	29.652
Escitalopram	Lexapro	SSRI	27.023
Fluoxetine	Prozac	SSRI	22.266
Bupropion	Wellbutrin	NDRI	20.184
Paroxetine	Paxil	SSRI	18.141
Venlafaxine	Effexor	SNRI	17.200
Citalopram	Celexa	SSRI	16.246
Trazodone	Desyrel	SRI	15.473
Amitriptyline	Elavil	TCA	13.462
Duloxetine	Cymbalta	SNRI	12.551
Mirtazapine	Remeron	TeCA	5.129
Nortriptyline	Pamelor	TCA	3.105
Imipramine	Tofranil	TCA	1.524

Notice how the numbers are increased overtime.

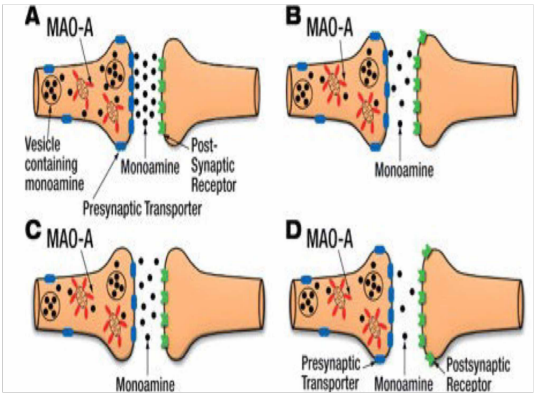
Drug name	Commercial name	Drug class	Total prescriptions
Sertraline	Zoloft	SSRI	33,409,838
Citalopram	Celexa	SSRI	27,993,635
Fluoxetine	Prozac	SSRI	24,473,994
Escitalopram	Lexapro	SSRI	23,000,456
Trazodone	Desyrel	SARI	18,786,495
Venlafaxine (all formulations)	Effexor (IR, ER, XR)	SNRI	16,110,606
Bupropion (all formulations)	Wellbutrin (IR, ER, SR, XL)	NDRI	15,792,653
Duloxetine	Cymbalta	SNRI	14,591,949
Paroxetine	Paxil	SSRI	12,979,366
Amitriptyline	Elavil	TCA	12,611,254
Venlafaxine XR	Effexor XR	SNRI	7,603,949
Bupropion XL	Wellbutrin XL	NDRI	7,317,814
Mirtazapine	Remeron	TeCA	6,308,288
Venlafaxine ER	Effexor XR	SNRI	5,526,132
Bupropion SR	Wellbutrin SR	NDRI	4,588,996
Desvenlafaxine	Pristiq	SNRI	3,412,354
Nortriptyline	Sensoval	TCA	3,210,476
Bupropion ER	Wellbutrin XL	NDRI	3,132,327
Venlafaxine	Effexor	SNRI	2,980,525
Bupropion	Wellbutrin IR	NDRI	753,516

- One of the weaknesses of the monoamine hypothesis is the fact that amine levels increase immediately with antidepressant use, but maximum beneficial effects of antidepressants are not seen for many weeks. **Why?**

  >> The time required to synthesize neurotrophic factors has been proposed as an explanation for this delay of antidepressant effects.

Neurotrophic Hypothesis

- Depression appears to be associated with a drop in brain- derived neurotrophic factor (BDNF) levels in the cerebrospinal fluid and serum as well as with a decrease in tyrosine kinase receptor B activity.
- BDNF is thought to exert its influence on neuronal survival and growth effects by activating the tyrosine kinase receptor B in both neurons and glia.
- Animal and human studies indicate that stress and pain are associated with a drop in BDNF levels and that this loss of neurotrophic support contributes to atrophic structural changes in the hippocampus and perhaps other areas such as the medial frontal cortex and anterior cingulate
- Studies suggest that major depression is associated with substantial loss of volume in the hippocampus, anterior cingulate and medial orbital frontal cortex.



Tricycle antidepressant (Amitriptyline)

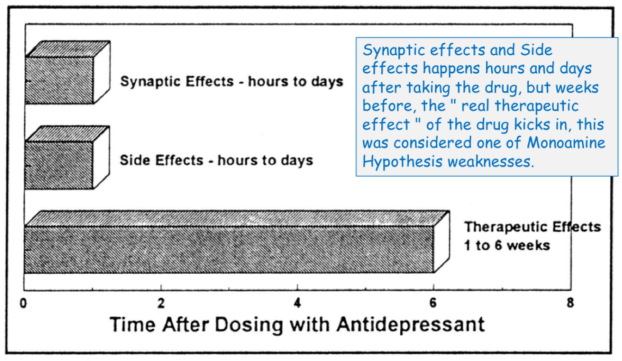
- TCAs inhibit serotonin, norepinephrine, and dopamine transporters, slowing reuptake.
- with a resultant increase in activity.
- Muscarinic acetylcholine receptors, alpha-adrenoceptors, and certain histamine (H1) receptors are blocked.

Side effects:

(1) drug-induced Sedation
(2) Orthostatic hypotension
(3) Cardiac effects
(4) Anticholinergeric effects dry mouth, constipation,blurred vision,urinary retention.

SSRIs (Serotonin-specific reuptake inhibitors)

- **inhibits the reuptake of serotonin without seriously effecting the reuptake of dopamine & norepinephrine.**
- ∅ **Most common side effects include GI upset*, sexual dysfunction (30%+!), anxiety, restlessness, nervousness, insomnia*, fatigue or sedation, dizziness It will take 1 week then disappears because of tolerance/adaptation for the GI effect**
  (No adaptation , we should decrease the dose or change the drug)
- ∅ **Can develop a discontinuation syndrome with agitation, nausea, disequilibrium and dysphoria**



Onset of action of antidepressants. Synaptic effects and side effects of antidepressants begin before therapeutic effects are observed.